UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,538	07/19/2001	Josephine Egan	14014.0346U1	5705

23859 7590 07/14/2003

NEEDLE & ROSENBERG, P.C.
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER
JIANG, DONG

ART UNIT	PAPER NUMBER
1646	15

DATE MAILED: 07/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,538	EGAN ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-21,23,25-27 and 29-52* is/are pending in the application.

4a) Of the above claim(s) *39-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-21,23,25-27 and 29-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-10,12-21,23,25-27 and 29-52* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED OFFICE ACTION

Applicant's amendment in paper No. 12, filed on 06 May 2003 is acknowledged and entered. Following the amendment, claims 11, 22, 24 and 28 are canceled, and claims 1, 4, 12, 15, 23, 27, 31-34 and 36 are amended.

Currently, claims 1-10, 12-21, 23, 25-27 and 29-52 are pending, and claims 1-10, 12-21, 23, 25-27 and 29-38 are under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 11, 22, 24 and 28 are moot as the applicant has canceled the claims.

The rejection of claims 1, 3-12, and 14-22 under 35 U.S.C. 101, for claiming non-statutory subject matter is withdrawn in view of applicant's amendment.

The rejection of claims 4, 15 and 37 under 35 U.S.C. 103(a) as being unpatentable over Rook et al. (1996) is withdrawn in view of applicant's amendments.

The rejection of claims 4, 15 and 37 under 35 U.S.C. 112, second paragraph, as being indefinite, made in the last Office Action, at pages 4 and 5, is withdrawn in view of applicant's amendment and argument.

The rejection of claims 32 and 33 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment and argument.

The prior art rejection of claims 1, 3-10, 12, 14-21 under 35 U.S.C. 102(b) as being anticipated by Eng, US 5,424,286 is withdrawn in view of applicant's amendment, and for the following reasons.

Eng teaches that both GLP-1 and exendin-4 are useful insulinotropic agent, and can be used in treatment of diabetes mellitus, and that bolus doses of GLP-1 or exendin-4 were given to the animals mimicking diabetes, and the isulinotropic response to GLP-1 or exendin-4 was demonstrated. Although Eng does not state explicitly the effect of GLP-1 or exendin-4 on converting non-insulin-producing cells into insulin-producing cells, such a converted population of cells *inherently* exists in the treated animals as the prior art consists of same steps described in

the present claims. The amendment with the addition of "*an isolated*" in claims 1 and 12 reads on cells in vitro. As such, the prior art reference no longer anticipates these claims, nor can it make it obvious as Eng does not teach the functional activity of GLP-1 or exendin-4 on converting non-insulin-producing cells into insulin-producing cells.

The prior art rejection of claims 1, 3-10 under 35 U.S.C. 102(b) as being anticipated by Dupre WO 95/31214 is withdrawn in view of applicant's amendment, and for the same reasons above.

The rejection of claims 2, 13, 29, and 25 under 35 U.S.C. 102(b) as being anticipated by Raufman et al. (J. Biol. Chem., 1992, 267(30):21432-27) is withdrawn in view of applicant's amendment.

New Matter Rejection:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 13, 25, 29, 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to claims 2, 13, 25, 29, the amended claims 1, 12, 23 and 27, from which claims 2, 13, 25 and 29 depend, recite the new limitation of "for at least twenty four hours", however, the specification indicates that the in vitro contacting of cells with GLP-1 is 3 days (Example 5, page 58, lines 7-8). The scope of at least twenty four hours and 3 days are different. Therefore, such amendment has changed the scope of the invention, and is not supported by the original disclosure. This is a new matter rejection.

With respect to claim 34 and the dependent claim 35, the amendment of claim 34 adds the new limitation of "a subject *lacking insulin-producing cells*". Applicants have not pointed out, nor can the Examiner locate, the basis in the specification for such a limitation. The prior

art rejection would be reinstated for claims 34 and 35 if new matter is deleted. The above rejection is a new matter rejection.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 12-21, 23, 25-27 and 29, 30, 32-38 remain rejected, and claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons set forth in the last Office Action, paper No. 10, mailed on 29 January 2003, at page 4.

Applicants argument, filed on 06 May 2003 (paper No. 12) has been fully considered, but is not deemed persuasive for reasons below.

At page 9 of the response, the applicant argues that the court held that the limitation "which produces substantially equal E and H plane illumination patterns" (*In Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819,6 USPQ2d 2010 (Fed. Cir. 1988)) was definite because a person of ordinary skill in the art would know what is meant by "substantially equal", and that applicants believe that a person of ordinary skill in the art, in light of the specification, would understand what is meant by the term "substantially homologous", which include one or more additions, deletions or substitutions in the amino acid sequence without appreciable loss of functional activity of the referenced amino acid sequence. This argument is not persuasive because in *In Andrew Corp. v. Gabriel Electronics*, the term "substantially equal" is used for describing a physical pattern, whereas the term "substantially homologous" in the instant claims is used to describe an amino acid sequence. As the amino acid sequence is the primary structural feature of a polypeptide, a skilled artisan would not be able to envision precisely the detailed structure of the encompassed proteins, which have "substantially homologous" sequence as that described in the claim limitation. A definition of "amino acid sequences substantially homologous" to GLP-1 or exendin-4 is noted at pages 15-16 of the specification, which indicates polypeptides including one or more additions, deletions or substitutions of amino acids. Such a

definition does not define the upper limit as to how many amino acids may be altered. Therefore, the metes and bounds of the claim still cannot be determined.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12-21, 23, 25-27 and 29, 30-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to an isolated population of insulin-producing cells made by contacting GLP-1 or exendin-4, does not reasonably provide enablement for claims to an isolated population of insulin-producing cells made by contacting growth factors having amino acid sequences *substantially homologous* to GLP-1 or exendin-4, or *fragment* thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claim limitation of "growth factors having amino acid sequences *substantially homologous* to GLP-1 (or exendin-4)" in claims 1, 12, 23, 27, 31-34, and 36, given the broadest interpretation, reads on any or all possible functional equivalents of GLP-1 or exendin-4 based on the definition in the specification, which defines such as polypeptides that include one or more additions, deletions or substitutions in the amino acid sequence without appreciable loss of functional activity as compared to GLP-1 or exendin-4 in terms of the ability to differentiate insulin-producing cells from non- insulin-producing cells (the paragraph bridging pages 15-16), and does not give upper limit as to the number of amino acid changes. As such, any functionally equivalent protein with no structure similarity to GLP-1 or exendin-4 would meet the limitation.

Enablement is not commensurate in scope with claims to any or all possible functional equivalents of GLP-1 or exendin-4. It is noted that the patentability of the claimed "growth factors" rests not on the biological property, but rather the particular sequences disclosed in the specification as filed because there exist other distinct proteins with the same or similar biological properties. Since there is no upper limit given as to the number of amino acid changes, *any* functionally equivalent polypeptide with no structure similarity to GLP-1 or exendin-4 would meet the limitation. Additionally, the specification provides no information about the relationship of the function and structure of GLP-1 and exendin-4, nor enough guidance to teach how to make a commensurate number of the claimed species without altering the biological property. Therefore, it is not predictable what essential structures are required for the protein to be functional, and it would require undue experimentation to determine such. It would require undue experimentation to determine such.

Due to the large quantity of experimentation necessary to determine growth factors having the claimed biological activity (functional equivalent of GLP-1 or exendin-4), the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to identify the sequence structure of said growth factor, and therefore embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Additionally, the Examiner notes that the description of claimed proteins via a biological function is similar to the situation in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) in which it was found that:

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt,* 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

In the current instance, the claims do not positively identify the protein of the invention by its sequence, but rather define such in terms of its biological activity. Therefore, the currently pending claims are analogous to the DNA claims in *Maizel*, in which the DNA was defined by the biological activity of the protein it encoded.

Claims 1, 12, 23, 27, 31-34, and 36 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "*growth factors having amino acid sequences substantially homologous to GLP-1 (or exendin-4), and fragment thereof*". However, the specification merely exemplifies a few growth factors capable of differentiating a non-insulin producing cell into a insulin producing cell, such as hepatocyte scatter factor and activin A, without specifying sequence similarity (page 15, lines 16-20), and there is no such a grow factor meeting the limitations of the claim is identified or particularly described in the specification .

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of IFN-γ, the skilled artisan cannot envision the detailed chemical structure of the encompassed stimulators of IFN-γ, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, no growth factor having amino acid sequence substantially homologous to GLP-1 or exendin-4 meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 26, 27, 30, 31 and 36-38 remain rejected, and claim 31 is under 35 U.S.C. 102(b) as being anticipated by Eng, US 5,424,286, for the reasons set forth in the last Office Action, paper No. 10, mailed on 29 January 2003, at page 6.

Applicants argument, filed on 06 May 2003 (paper No. 12) has been fully considered, but is not deemed persuasive for reasons below.

At pages 13-18 of the response, the applicant argues that MPEP requires the Examiner to provide a rationale or evidence tending to show inherency, and the prior art does not inherently anticipate the claimed invention, in view of several case laws, and that claims 1, 12, 23, 27 and 31 are amended by adding "for at least 24 hours", and thus the prior art reference, the '286 patent, does not expressly disclose each and every element of the amended claims. These arguments are not persuasive for the following reasons.

With respect to case laws for the argument of inherency, they do not apply in the instant situation. For example, in *In re Zierden*, 162 USPQ 102 (CCPA 1969), it is pertained to a method of removing alluvium from industrial waters, and is totally irrelevant to the method of converting non-insulin producing cells into insulin producing cells. Additionally, as the

industrial waters may contain different ingredients, which may not be removed by the same method, teachings regarding the removal of one specific element may not inherently teach the removal of a different chemical entity. In contrast, in the present situation, the individuals or the cells being treated have the same anatomic structures and biochemical components, therefore, as the active ingredient and the method steps used are the same between the prior art and the present invention, the results or the consequences would be inherently the same. It is unclear how and why they should or could be different otherwise.

With respect to the newly added claim limitation of "at least twenty-four hours", even though Eng does not mention explicitly that contacting the cells with GLP-1 *for at least 24 hours*, it is inherent as the method steps and the mean of administration are the same as that of the present invention. Further, the contacting in the prior art has to be at least 24 hours because there is no way to take the GLP-1 away once it is injected into a subject.

Further, with respect to the new limitation of "a method of *inducing insulin secretion*" in claim 36, as Eng teaches that GLP-1 and exendin-4 are useful *insulinotropic* agents, indicating a function in inducing insulin secretion, and therefore, the method of treating diabetes with GLP-1 or exendin-4 taught in the reference still anticipates the claim.

Claims 23, 26, and 31 remain rejected under 35 U.S.C. 102(b) as being anticipated by Dupre (WO 95/31214, provided by applicants), for the reasons set forth in the last Office Action, paper No. 10, mailed on 29 January 2003, at page 7.

Applicants argument in paper No. 12, pages 20-23, has been fully considered, but is not deemed persuasive for reasons above as some arguments are based on the same ground as above ("at least 24 hours", and the inherency), and for the reasons below.

At page 22 of the response, the applicant argues that the prior art reference teaches that GLIP can be used to treat diabetes who can still secrete insulin based on two different mechanisms, and does not teach the use of GLIP for treating diabetic patients no longer have endogenous insulin secretion, and differentiating non-insulin-producing cells into insulin-producing cells. This argument is not persuasive because although the prior art reference does not mention the mechnism of GLIP on differentiating non-insulin-producing cells into insulin-

producing cells, a newly discovered mechanism does not make the product novel, nor change the outcome of a method with the same method steps. Further, the present claims do not comprise the requirement that the treated subject no longer has endogenous insulin secretion.

Applicants further argue that the prior art reference teaches administering GLIP in a two hour infusion, and in contrast, the instant application teaches a contact for at least 24 hours. This argument is not persuasive because, as mentioned above, there is no way to stop contacting once the drug is administered under said circumstance, and thus if a bolus injection, for example, is sufficient to serve the purpose, a two hour infusion would be able to do the same.

Claim 31 remains rejected under 35 U.S.C. 102(b) as being anticipated by Mashima et al. (Endocrinology, 1996, 137(9): 3969-76, provided by applicants), for the reasons set forth in the last Office Action, paper No. 10, mailed on 29 January 2003, at page 7.

Applicants argument in paper No. 12 has been fully considered, but is not deemed persuasive for reasons above (with respect to the new limitation of "at least 24 hours", and the inherency), and for the reasons below.

At page 24 of the response, the applicant argues that the amendment overcomes the rejection. This argument is not persuasive because the addition of "growth factors having amino acid sequences substantially homologous to ..." is not sufficient based on the present disclosure. The specification defines "amino acid sequences substantially homologous" to GLP-1 or exendin-4 as that polypeptides including one or more additional amino acids, deletions of amino acids, or substitutions in the amino acid sequence of GLP-1 or exendin-4 without appreciable loss of functional activity in terms of the ability to differentiate insulin producing cells (the paragraph bridging pages 15 and 16). Mashima's hepatocyte growth factor (HGF) meets such a definition as there is no limitation in the definition as to how many amino acids in the sequence can be added, deleted or substituted.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
6/26/03